REMARKS

Claims 1-11, 13, 14, 18, 19, and 25-62 were preciously cancelled. Claim 21 was previously withdrawn. Applicants reserve the right to file divisional and continuation applications directed towards the cancelled and withdrawn subject matter. Claim 12 has been amended. Support for the amendment can be found throughout the specification, specifically at page 9, line 3 - page 13, line 3 and page 17, lines 18-23 of the originally filed specification (paragraphs [0024] - [0032] and [0055] of the published version of the specification (U.S. Patent Application Publication No. 20040171527)). No new matter has been added. Claims 12, 15-17, 20, 22-24, 63, and 64 are currently under consideration.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 12, 15-17, 20, 22-24 and 63-64 are rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the enablement requirement for the reasons articulated in the previous Office Action. In response to Applicants' previously submitted arguments, the Examiner states that there is no teaching in the specification of the treatment of HCV infection with glycolipids. The Examiner continues in stating that Applicants' invention is limited to the finding of an association between Gaucher's disease and HCV. See Office Action page 4.

Applicants respectfully traverse the rejection and maintain that claims 12, 15-17, 20, 22-24 and 63-64 are fully enabled by the specification. The enablement requirement of § 112 is satisfied when an application describes a claimed invention in a manner that permits one of ordinary skill to practice it, without undue experimentation. MPEP § 2164.01. Thus, the mere fact that experimentation *might* be required is insufficient to support an enablement rejection. Further, even complex experimentation is not necessarily undue. MPEP § 2164.01.

Applicant respectfully submits that no experimentation is required to make and use the invention of claim 1. Nonetheless, even if experimentation might be required, it would not be undue. In this regard, it is important to be mindful that the question of enablement is one of predictability in view of what is known in the art. Consequently, the amount of guidance or direction needed to satisfy the enablement requirement is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. MPEP § 2164.03.

The specific question of whether experimentation is "undue" is determined based on the following eight Wands factors:

1. Breadth of the claims;
2. Nature of the invention;
3. State of the prior art;
4. Level of ordinary skill in the art;
5. Predictability of the art;
6. Amount of direction provided in the specification;
7. Any working examples; and
8. Quantity of experimentation needed relative to the disclosure.

MPEP § 2164.01(a), citing In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Further, a proper analysis of whether any experimentation is undue requires an analysis of all of the pertinent *Wands* factors. (MPEP § 2164.01(a)). It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. Id..

Applicants continue to assert that the claims satisfy the enablement requirement. However, solely in an effort to expedite prosecution, claim 12 (the sole independent claim) has been amended to recite a process for treating a disease in a mammalian subject comprising administering to said subject an effective amount of an intermediary metabolite or a reagent that increases the intracellular or extracellular or serum level of a mammalian intermediary metabolite in said subject, where such increase results in a change in the immune profile of subject. As taught in the specification, such immune parameters may include cellular, humoral or cytokine elements, and the modulation or change can be specific or non-specific.

With regard to the *Wands* factor of "Nature of the Invention", Applicants respectfully assert that amended independent claim 12 is now directed towards a method for treating HCV comprising administering an effective amount of an intermediary metabolite or a reagent that increases the intracellular or extracellular or serum level of a mammalian intermediary metabolite in said subject, the increases resulting in a change in the immune profile of subject,

and wherein said disease is cancer, a viral infection, or an autoimmune disease.

With regard to the *Wands* factor of "Breadth of the Claims", the Examine states that "The claims encompass all cancer, viral infections or autoimmune diseases..." Applicants disagree with the Examiners conclusion that the claims are overly broad. Applicants wish to remind the Examiner that Applicants elected the virus of HCV in the response to restriction requirement filed August 2, 2005.

Considering the *Wands* factor of "Presence or absence of Working Examples and Amount of Direction or Guidance Present", Applicants respectfully disagree with the Examiner's statements that "Contrary to applicant's assertion that Applicant 'clearly teaches the administration of glycolipids for the treatment of HCV infection', no such teaching can be found in the specification." See Office Action, page 4. It appears that the Examiner makes this conclusion because "The specification does not contain any working examples **evidencing** to the skilled artisan that the administration of glycolipids treats HCV infection." See Office Action, page 4 (emphasis added). Applicants respectfully direct the Examiner's attention to the following passages (page 14, line 24 - page 15, line 16 of the originally file specification; paragraphs 38 - 40 of the published version of the specification (U.S. Patent Application Publication No. 20040171527)):

> [0038] In one embodiment, this invention provides a process for treating a disease in a mammalian subject, e.g. a human, in which an effective amount of a mammalian intermediary metabolite or reagent is administered to the subject. By doing so, the intracellular or extracellular or serum level of the metabolite in the subject is raised. The intermediary metabolite can comprise lipids or conjugated biomolecules. The latter can take the form of glycolipids, lipoproteins and glycoproteins other than antibodies, cytokines or hormones. Such glycolipids can, in turn, comprise a monosaccharide ceramide, e.g. glucosyl ceramide or galactosyl ceramide.
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> [0039] Administration of the intermediary metabolite or reagent, as described further below, can be carried out by conventional means known in the art, including intravenous means, intramuscular means, or oral means

> [0040] In terms of the diseases that can be treated in accordance with the present invention, these include cancers, infections and immune dysfunctions. Infections can be varied and include those whose etiology is viral or bacterial in nature. Viral infections include, for example, HBV, HCV and HIV.

Applicants assert that the above passages indicate that HCV as an appropriate disease candidate for the methods of the current invention. These passages also indicate that glycosylceramides are appropriate reagents to carry out this treatment. The specification states that: (1) HCV is an appropriate disease target: (2) the administered compound is a glycolipid; and (3) treatment consists of administration of the glycolipid. In addition, the specification describes experimental results showing that glycolipids cause a change in the immune profile of subject. See, for example, page 9, line 3 - page 13, line 3 and page 17, lines 18-23 of the originally filed specification (paragraphs [0024] - [0032] and [0055] of the published version of the specification (U.S. Patent Application Publication No. 20040171527)).

Although the specification contains no working examples, data is included illustrating the immune profiles of normal and Gaucher patients that are either infected or uninfected with HCV. This data allowed the inventors to conclude that emulation of the Gaucher condition, i.e., artificially heightened levels of glycolipids, would emulate the beneficial immune responses to HCV which are similar to that of a Gaucher patient. As such, the artificial administration of glycosylceramides to HCV patients to achieve such a result is in the nature of a prophetic example. See originally filed specification at page 9, line 3 - page 13, line 3 and page 17, lines 18-23 (paragraphs [0024] - [0032] and [0055] of the published version of the specification (U.S. Patent Application Publication No. 20040171527)).

In response to Applicants' previously submitted response, the Examiner states that "Applicant is reminded that enablement is not directed at establishing that the claimed invention will not work." See Office Action page 5. Applicants assert that the issue of the lack of evidence that the invention will not work is very germane to the purported lack of enablement. If the invention functions as described by the specification, one of skill in the art would only be required to perfect the dosage and means of administration of the glycolipid. As acknowledged by the Examiner in a previous Office Action, such actions constitute routine experimentation in

the art.

The Examiner states on page 6 of the Office Action: "Moreover, it is noted that the specification contains neither an in vitro nor an in vivo study demonstrating that glycolipids treat HCV infection" and "Applicant has not demonstrated that glycolipids treat HCV." The Examiner then states "Thus for a skilled artisan to practice the claimed invention the skilled artisan would have to demonstrate that glycolipids treats HCV..." Id. A specific demonstration that glycolipids treat HCV infection is not required to practice the invention. The Examiner further states that "the skilled artisan would not be able to demonstrate that glycolipids treat HCV without undue experimentation." These statements concern issues in evaluating the results of the treatment **after** carrying out the present invention, rather than the ability of a skilled artisan to use the invention. Events which occur after practicing a claimed method are not an element of a proper *Wands* analysis.

The Examiner again comments on the lack of working examples on page 7 of the Office Action in stating "Yet, it is noted that Applicant has not taught nor demonstrated to the skilled artisan that the administration of any glycolipids treats HCV". Applicants assert that this statement is only a partially correct in that the specification teaches the administration of glycolipids for treatment of HCV by affecting a change in the immune profile of a subject (as evidenced from the quoted passages) but does not demonstrate the administration of glycolipids as being effective in treating HCV. It appears that the Examiner is concluding that the enablement requirement would be satisfied only if the specification: (1) contained a physical demonstration that administration of a glycolipid was beneficial in treating HCV; (2) described experiments characterizing the roles of innate and antigen-specific immune responses to HCV; or (3) described "a specific immune parameter that particular metabolite/glycolipid modulates and how the modulation results in the treatment of HCV." See Office Action, page 8. Prophetic exemplification is considered appropriate unless there is definitive evidence that the method will not work as described or it there is insufficient teachings of how to accomplish the method. MPEP 2164.02. As discussed above, the desired result of the present claims (treatment of HCV and altering the immune profile of a subject) would be accomplished by the single step of administration of the appropriate dosage of a glycolipid. In addition, the claims contain no

limitation concerning innate or antigen-specific immune response. Further characterization of these effects is not necessary in practicing the invention nor would the lack of further characterizations hinder carrying out the present invention. Applicants also assert that the claims do not require the presence of a mechanism describing how administration modulates the immune system. Figures 1 - 6 demonstrate several altered immune parameters in Gaucher patients which appear to decrease detrimental effects caused by the immune response to HCV infection. It is expected that one or more of these same parameters will be beneficially altered in HCV patients.

In addition, methods for evaluating the success or lack of success in treatment of HCV or its symptoms are known to one of skill in the art. Such methods are routinely utilized in clinical trials with humans and chimpanzees and would require no undue experimentation. Applicants' previous response cited to a pending patent application describing the use of the primitive primate Tupaia as a potential alternative. Lastly, parameters used to judge efficacy (i.e., evaluating success) are well known in the art given the amount of research available in evaluating potential approaches to treat HCV.

The Examiner comments on page 8 of the Office Action that "There is no information provided in the specification regarding the specific immune parameter that a particular metabolite/glycolipid modulates and how the modulation results in the treatment of HCV." These parameters are discussed as follows (page 17, lines 18-23 of the originally file specification; paragraph 55 of the published version of the specification (U.S. Patent Application Publication No. 20040171527)):

> [0055] Yet another aspect of the present invention is a process for treating a disease in a mammalian subject, e.g., a human, comprising the step of administering to the subject an effective amount of a mammalian metabolite so as to modulate or change at least one component in the immune system of the subject. Such an immune system component can comprise cellular, humoral or cytokine elements, and the modulation or change can be specific or non-specific.

In regards to the *Wands* factor of "State of the Prior Art", the Examiner on pages 5-6 of the Office Action comments on the lack of characterization of innate and antigen specific

immune responses. This alleged "lack of characterization" does not appear to be relevant to the question of whether a skilled artisan has the ability to practice the present invention. The only advantage of further characterization of these parameters would be for the development of theoretical predictions. An inability to link the effects of glycolipids to innate and antigen specific immune response to HCV does not affect the claimed method of increasing intracellular or extracellular serum levels of an intermediary metabolite resulting in a change in the immune profile. A lack of a complete characterization of these factors will not disallow administration of a glycolipid, i.e., a more clear and complete understanding will not assist a skilled artisan in the administration of a glycolipid to change immune parameters. It is unclear to Applicants what particular challenges of administering glycolipids to an HCV infected subject are raised by the absence of a complete characterization of immune response to HCV.

The Examiner further states on page 9 of the Office Action:

> Applicant teaches that metabolites such as glycolipids modulate the immune profile, however, such does not commensurate with the claimed invention. The claimed invention is not directed at a method of modulating an immune response in an HCV infected person. Rather, the claimed invention is directed at a method of treating HCV in an infected person.

Applicants respectfully assert that the claimed invention is directed to a method of treating an HCV infected person by increases the intracellular or extracellular or serum level of a mammalian intermediary metabolite in said subject, said increases in the intracellular or extracellular or serum level of a mammalian intermediary metabolite resulting in a change in the immune profile of subject. As stated above, practice of the invention does not require an investigation into the particular mechanisms that would eventually result in the beneficial result that is desired. Administration of the compound intrinsically causes a series of events that take place for which the practitioner has no further control after the administration step (such as a change in the immune profile of the subject). A lack of knowledge of this mechanism does not hinder the skilled artisan in practicing the present invention, nor does possession of such information engender any particular increased ability. The only advantage of having such

knowledge would be the potential increase in confidence by the Examiner that the invention would work as claimed by the inventors.

For example, a claim that recites "A method for relieving fever comprising administration of aspirin" would not require knowledge of a mechanism relating to vasoconstriction or how aspirin would induce such an effect. In addition, a claim that recites "A method of lowering the clotting level of blood by administration of aspirin" would not require knowledge of the blood cascade or the particular target of aspirin. Practice of the method of either of these exemplary claims would only entail administration of a compound that had the particular structure of aspirin using the appropriate dosage. Apart from this, proving that such methods would be effective (for example, for FDA approval) would subject Applicants to a different standard and require clinical evidence demonstrating the adequacy of achieving the desired benefits.

In view of the foregoing, Applicant respectfully submits that ordinarily skilled artisans would be able to make and use the claimed invention, despite any experimentation that might be required. The specification contains examples of a change in the immune profile of a subject due to the presence of increased levels of glycolipids (page 14, line 24 - page 15, line 16 of the originally file specification; paragraphs 38 - 40 of the published version of the specification (U.S. Patent Application Publication No. 20040171527)). In addition, methods for evaluating the effectiveness of an HCV treatment are well known to one of skill in the art. Thus, this conclusion is buttressed by the amount of knowledge in the state of the art and the majority of *Wands* factors that weigh in favor of enablement. Therefore, the present application adequately enables the claimed invention.

Applicant thus respectfully requests favorable reconsideration and withdrawal of the rejection under 35 U.S.C. § 112.

Conclusion

It is believed that claims 12, 15-17, 20, 22-24, 63, and 64 are now in allowable form. Accordingly, a timely Notice of Allowance to this effect is earnestly solicited.

The Examiner is invited to contact the undersigned at 412-918-1116 to discuss any matter concerning this application.

The Office is hereby authorized to charge any additional fees or credit any overpayments under 37 C.F.R. § 1.16 or § 1.17 to the previously authorized deposit account number 50-0525.

Respectfully submitted,

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